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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,479	10/08/2003	Yin-Xiong Li	5405-295	7768

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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,479	LI ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11 and 13-24* is/are pending in the application.

4a) Of the above claim(s) *9 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,11,13-17 and 19-24* is/are rejected.

7)☒ Claim(s) *6,7,16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed November 8, 2006. Claims 1-24 were previously pending, with claims 9 and 18 withdrawn from consideration. Applicants cancelled claims 2 and 12 and amended claims 1, 3, 11, 13 and 24. Claims 1, 3-11 and 13-24 are pending, with claims 9 and 18 withdrawn from consideration.

2. Applicants' amendments overcame the following rejections: rejection of claim 24 under 35 U.S.C. 112, second paragraph; rejection of claims 1, 6-8, 11, 16, 17 and 20-23 under 35 U.S.C. 102(b) as anticipated by Zohlnhofer et al.; rejection of claims 1, 7, 8, 11, 17 and 20-23 under 35 U.S.C. 102(e) as anticipated by Mueller et al.; rejection of claims 10, 19 and 24 under 35 U.S.C. 103(a) over Mueller et al., Weissman et al. and Lasken et al.

3. Applicants' submission of a new drawing and amendment to the specification obviated the objection to drawings presented in the previous office action.

4. Applicants' submission of a new abstract obviated the rejection presented in the previous office action.

5. This office action is made non-final because of new grounds for rejection.

Claim Objections

6. Claims 6, 7, 16 and 17 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 6 and 16 are drawn to the methods of claims 1 and 11, respectively, where the step of linking a second known segment is accomplished by ligating it using RNA ligase. However, Applicants amended claims 1 and 11 to include the limitations of attaching the second known

segment using a bridging primer. Therefore, claims 6 and 16, and their dependent claims 7 and 17 do not further limit claims 1 and 11.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3-5, 8, 11, 13-15 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Chenchik et al. (U.S. Patent No. 5,962,272 A).

Claims 1, 3, 8, 11 and 13 will be considered together in claim 13, which is a species of claims 1, 3, 8 and 11.

Regarding claims 1, 3, 8, 11 and 13, Chenchik et al. a method of amplifying a plurality of different mRNA targets in a sample (col. 3, lines 9-11), the method comprising:

(a) binding a first primer to a each of said target mRNA, the first primer comprising, in the 5' to 3' direction, a first known segment and an oligo T segment (Fig. 1; Fig. 3; col. 3, lines 25-38; col. 10, lines 8-59);

(b) transcribing a cDNA from said each of said target mRNA by elongation of said first primer with reverse transcriptase (Fig. 1; Fig. 3; col. 3, lines 25-38; col. 9, lines 22-51); then

(c) linking a second known segment to the 3' terminus of each of said cDNAs (Fig. 1; Fig. 3; col. 3, lines 40-52); and then

(d) uniformly amplifying each of said cDNAs with a pair of primers, one of which pair binds to said first known segment and the other of which pair binds to said second known segment (Fig. 3; col. 4, lines 20-35); wherein:

said step of transcribing a cDNA from each of said target mRNAs is followed by the step of adding at least one additional predetermined residue to the 3' terminus of each of said cDNAs with a terminal deoxynucleotidyl transferase (col. 6, lines 54-61); and

said step of linking a second known segment to the 3' terminus of said cDNAs is carried out by:

(i) binding a second bridge primer to each of said cDNAs, said second primer comprising, in the 5' to 3' direction, a second known segment and at least one corresponding residue, which corresponding residue binds to said at least one additional predetermined residue by Watson-Crick pairing, said second primer having an inactivated residue on the 3' terminus thereof (Fig. 1; Fig. 3; col. 3, lines 40-52; col. 5, lines 50-67; col. 6, lines 1-34 and 61-67; col. 7, lines 1-3; col. 8, lines 7-18 and 25-28); and then

(ii) further transcribing said cDNAs from said second bridge primer by elongation of said at least one additional predetermined residue with reverse transcriptase so that a plurality of cDNAs is produced having said first known segment on the 5' terminus thereof and said second known segment on the 3' terminus thereof (Fig. 1; Fig. 3; col. 3, lines 40-52; col. 5, lines 50-67; col. 6, lines 1-34 and 61-67; col. 7, lines 1-3).

Regarding claims 4, 5, 14 and 15, Chenchik et al. teach unmatched C residues and corresponding G residues (col. 6, lines 54-67).

Regarding claim 21, Chenchik et al. teach amplification of 10-100 ng of total RNA (col. 15, lines 29-31).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 10, 19 and 24 are rejected under 35 U.S.C. 103(a) over Chenchik et al. (U.S. Patent No. 5,962,272 A), Weissman et al. (U.S. Patent No. 6,235,502) and Lasken et al. (U.S. Patent No. 6,323,009).

A) The teachings of Chenchik et al. are presented above. They teach amplification by PCR, but do not teach rolling circle amplification. They do not teach that the first and second known segments are the same.

B) Weissman et al. teach amplification of linear DNA sequences by rolling circle amplification by adding adapters with identical sequences to the ends of DNA and then amplifying the resulting circles with a single primer (Fig. 2; col. 4, lines 56-67; col. 5, lines 1-3).

C) Lasken et al. teach amplification of circular DNA targets using rolling circle amplification with multiple primers (Fig. 1; col. 3, lines 41-60; col. 4, lines 66, 67; col. 5, lines 1-11; col. 6, lines 50-67; col. 7, lines 1-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have converted the linear fragments of Chenchik et al. into circles by the method of Weissman et al. which could be amplified by rolling circle amplification of Lasken et al. The motivation to do so, provided by Lasken et al., would have been that the amplification could be carried isothermally, was low cost, had high sensitivity and flexibility, and low risk of contamination (col. 2, lines 8-16) and allowed sequence determination from as little as 0.01 ng of circular template (col. 4, lines 51-57).

11. Claims 6, 7, 16, 17, 20, 22 and 23 are rejected under 35 U.S.C. 103(a) over Chenchik et al. (U.S. Patent No. 5,962,272 A) and Zohlnhofer et al. (WO 2001/71027; cited in the previous office action).

A) Regarding claims 6 and 16, Chenchik et al. do not teach attaching the segments using RNA ligase. Regarding claims 20 and 23, Chenchik et al. teach amplification of nanogram quantities of RNA, but do not teach amplification of mRNA from fewer than 100 cells. Regarding claims 22 and 23, Chenchik et al. do not teach determination of the quantity of cDNAs.

B) Regarding claims 6 and 16, Zohlnhofer et al. teach attachment of the tails using RNA ligase (page 1, first paragraph; page 5, second paragraph).

Regarding claims 7 and 17, Zohlnhofer et al. teach segments comprsing DNA (page 1, first paragraph; page 5, second paragraph; page 8, first and second paragraphs).

Regarding claim 20, Zohlnhofer et al. teach amplification of mRNA extracted from a single cells or a few cells (page 10, second paragraph; page 29, first paragraph).

Regarding claim 22 and 23, Zohlnhofer et al. teach quantitation of the amplified DNA (page 12, second and fourth paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used amplification of a single cell or a few cells of Zohlnhofer et al. in the method of Chenchik et al. The motivation to do so, provided by Zohlnhofer et al., would have been, as stated by Zohlnhofer et al. (page 2, page 3, first paragraph):

"However, a plethora of physiological and/or pathological conditions would require to study the gene expression pattern or "transcriptome", defined as the entirety of mRNA molecules in a given biological sample (Velculescu, Cell, 88, 243-251 (1997) of a lower number of cells or even a single cell. For instance, the investigation of spatially and temporally regulated gene expression in embryogenesis would clearly profit from a method were a low number of cells, in particular a single cell, can be deduced. Similarly, it would be of high interest to investigate the gene expression pattern/transcriptome of individual cells or a low number of cells derived from adult tissue, like, inter alia, blood or neuronal (stem) cells. Furthermore, multiple pathological conditions could be clarified, e.g., the delineation of deregulated gene expression in a typical proliferation, mutaplasia,

preneoplastic lesians and/or carcinomata in situ. Other examples of locally restricted pathological processes which could be investigated comprise, but are not limited to, restenosis, Alzheimer's disease, Parkinson's disease, graft-versus-host disease or inflammations in autoimmunity. Furthermore, occult micrometastasis derived from a small cancer has dire consequences if the disseminated tumor cells survive in distant organs and grow into manifest metastases. Tumor cells left after resection of primary tumors are currently detected in bone marrow aspirates by immunocytochemical staining with antibodies directed against cytokeratins (reviewed in Pantel, J. Natl. Canc. Inst. 91, 1113-1124 (1999)). While several studies have established the prognostic significance of cytokeratin-positive micrometastatic cells in bone marrow (Braun, N. Engl. J. Med. 342, 525-533 (2000); Pantel, J. Natl. Canc. Inst. 91, 1113-1124 (1999)), the biology of these cells has largely remained enigmatic because of their extremely low frequency in the range of 10^{-5}-10^{-6}."

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637
Teresa Strzelecka
1/12/07